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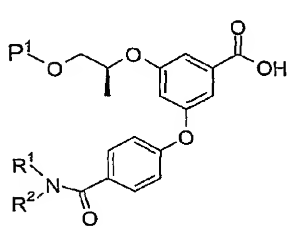
(54) Title: CHEMICAL PROCESS



(I)

(57) Abstract: A process for making a compound of formula (I), (A chemical compound should be inserted here - please see paper copy enclosed herewith) (I) which is useful as an intermediate to compounds which activate glucokinase, is described, (wherein P1, R1 and R2 are as defined in the description).

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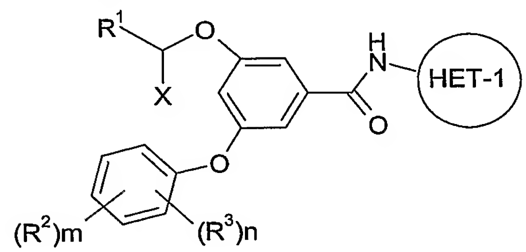
CHEMICAL PROCESS

This invention relates to an improved chemical process for making compounds which are useful in the treatment or prevention of a disease or medical condition mediated through glucokinase (GLK or GK), leading to a decreased glucose threshold for insulin secretion. Such compounds are predicted to lower blood glucose by increasing hepatic glucose uptake. Such compounds may have utility in the treatment of Type 2 diabetes and obesity. The invention is also related to intermediates useful in the improved chemical process.

In our applications (WO2005/080359, WO2005/080360, WO 2005/121110 (PCT/GB2005/002166), WO 2006/040529 (PCT/GB2005/003890) and WO 2006/040528 (PCT/GB2005/003888)) we have described compounds which are useful as GLK activators, which are of general chemical formula (A).



(A)

wherein for example

R^1 is hydroxymethyl, methoxymethyl or methyl;

X is methyl or ethyl;

R^2 is selected from $-C(O)NR^4R^5$, $-SO_2NR^4R^5$, $-S(O)_pR^4$ and HET-2;

HET-1 is an optionally substituted 5- or 6-membered, C-linked heteroaryl ring containing a nitrogen atom in the 2-position;

HET-2 is an optionally substituted 4-, 5- or 6-membered, C- or N-linked heterocyclyl ring containing 1, 2, 3 or 4 heteroatoms;

R^3 is selected from halo, fluoromethyl, difluoromethyl, trifluoromethyl, methyl, methoxy and cyano;

R^4 is selected from hydrogen, (1-4C)alkyl [optionally substituted], (3-6C)cycloalkyl (optionally substituted) and HET-2;

R^5 is hydrogen or (1-4C)alkyl;

or R^4 and R^5 together with the nitrogen atom to which they are attached may form a heterocyclyl ring system;

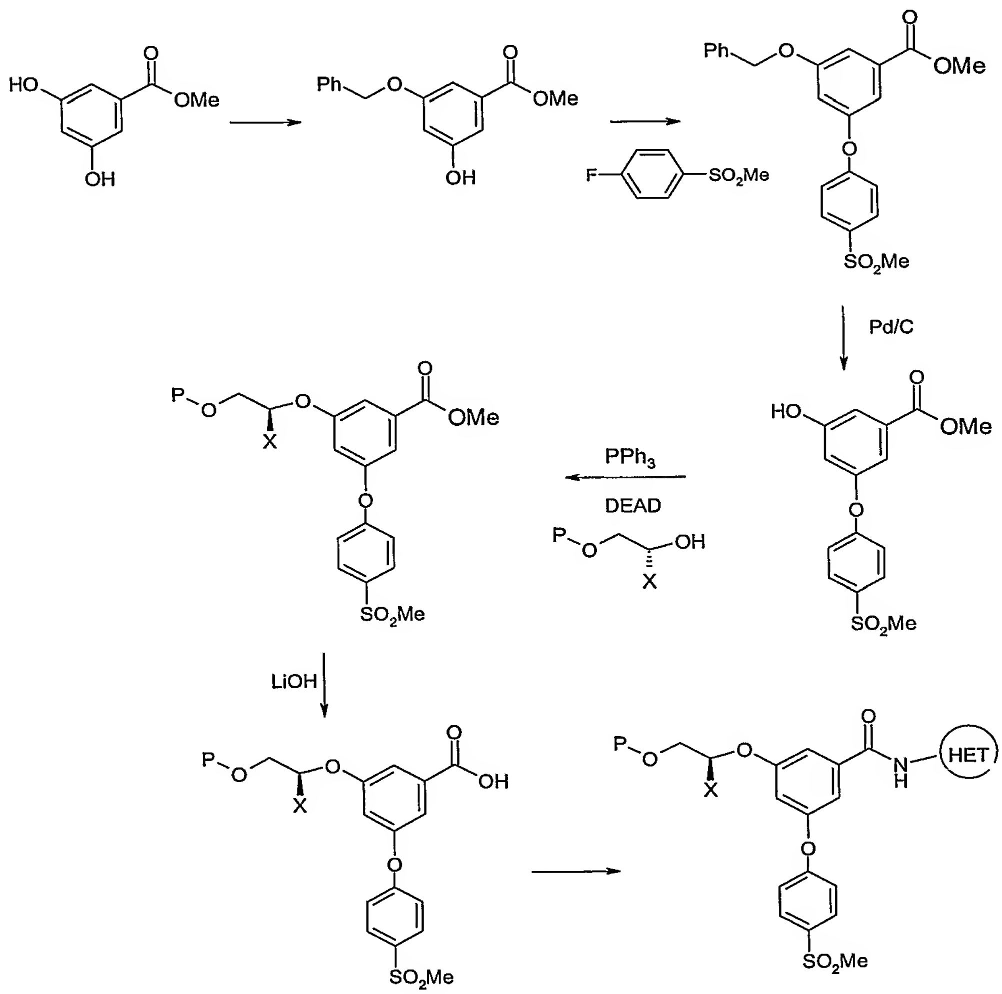
m is 0 or 1;

n is 0, 1 or 2;

provided that when m is 0, then n is 1 or 2;

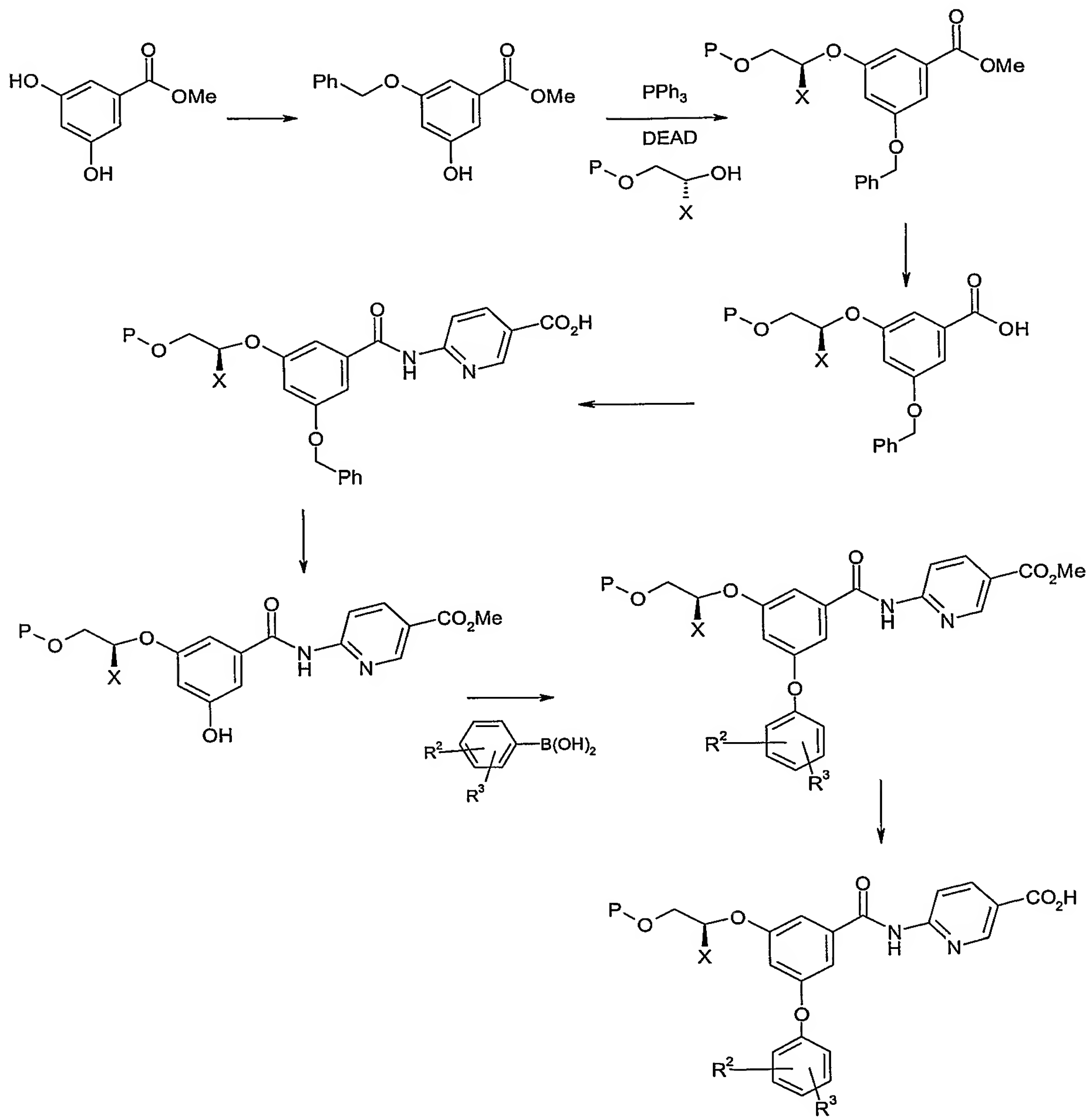
or a salt, pro-drug or solvate thereof.

The compounds of formula (A) are N-heterocyclyl-aryl amides, wherein the aryl ring is 3,5-disubstituted by a substituted alkyl ether and an aryloxy substituent. These compounds have for example been synthesised using reaction sequences such as those illustrated in Schemes 1 and 2 below:



Scheme 1

where X is as defined in Formula (A), P is methyl or a protecting group such as a trialkylsilyl group.

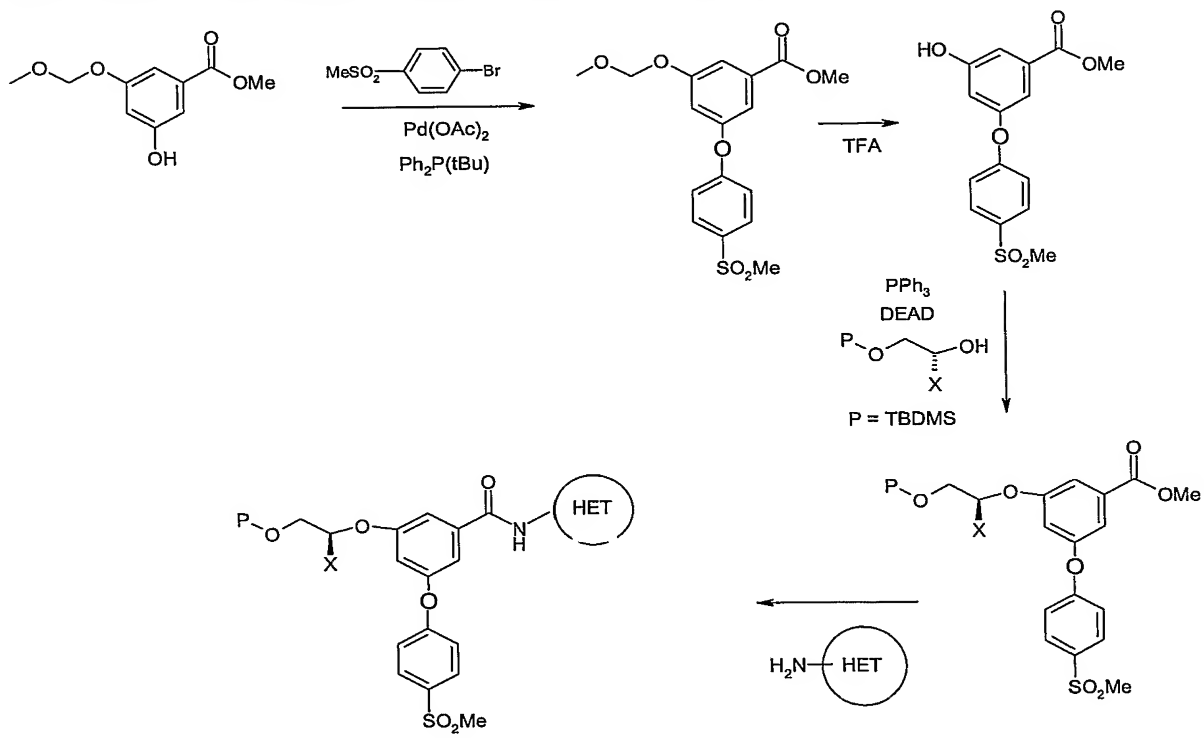


Scheme 2

The starting material for both of these synthetic routes is methyl(3,5-dihydroxy)benzoate. The order of attaching the various substituents around the phenyl ring has varied, but in both routes illustrated, it has been necessary to use protecting groups (benzyl in Schemes 1 and 2) during the synthetic sequence in order to differentiate between

the two hydroxy groups in the starting material. This inevitably introduces extra synthetic steps with the consequent implications for increased cost per unit weight of final product and increased waste and environmental impact, if the product were to be manufactured on significant scale.

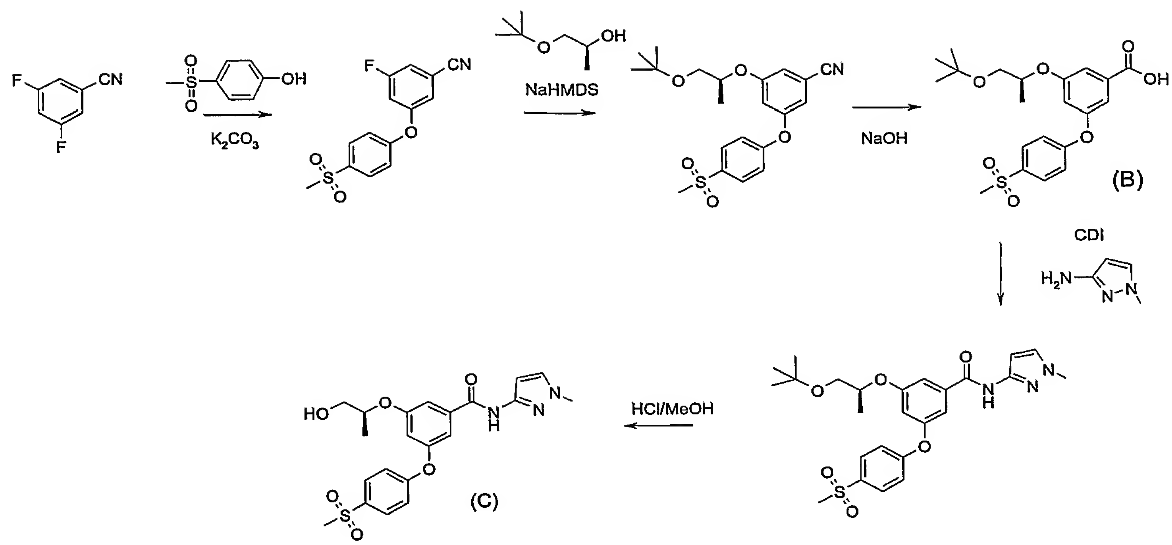
Concurrently, compounds with a similar general formula have been published (WO 2004/076420). A route used to these compounds is illustrated in Scheme 3.



Scheme 3

However, as shown above, a methoxymethyl protecting group is still utilised in this route.

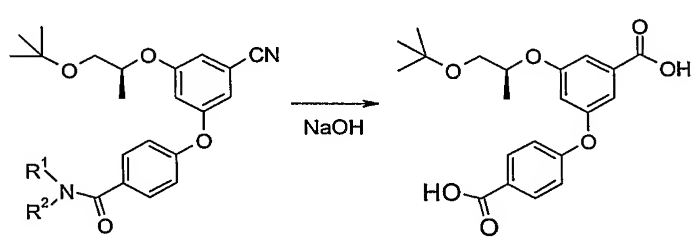
In order for such compounds to be useful commercially, there is a need to develop one or more short, efficient synthetic routes. In our co-pending PCT application PCT/GB2005/003882 we have described routes to the above compounds starting from dihalophenyl derivatives, which were exemplified, inter alia, according to the scheme below:



Scheme 4

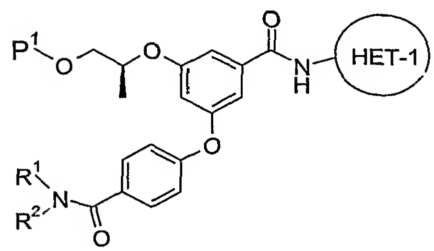
A key intermediate in this process is the benzoic acid derivative (B). Use of this intermediate provides rapid access to a number of heterocyclic amide analogues (such as compound (C)) by formation of the heterocyclic amide bond (illustrated above by the heterocycle being methylpyrazole).

Synthesis of intermediates of analogous structure to (B), where the methylsulfonyl group has been replaced by an amide, provides further challenges. For example, the conversion of the nitrile group to the carboxylic acid group of (B) using reagents such as sodium hydroxide may cause at least partial hydrolysis of the amide R^1R^2N-CO- as shown below:



Although the conversion of the nitrile to the desired carboxylic acid derivative, such as (B), may work to some useful degree, it would be advantageous to develop routes to compounds analogous to compound (B) which can tolerate the presence of sensitive substituents such as amides, to give high yields of the required carboxy intermediate, on a significant scale, for further elaboration to the final product (D) (wherein HET-1 is an

optionally substituted 5- or 6-membered, C-linked heteroaryl ring containing a nitrogen atom in the 2-position):



(D)

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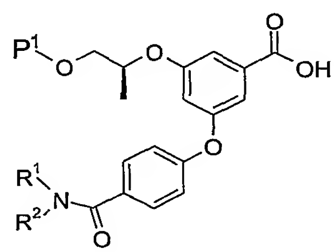
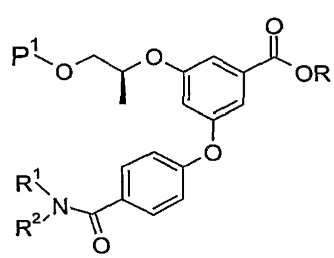
According to a first aspect of the invention, there is provided a process for making a compound of formula (I),



(I)

said process comprising either:

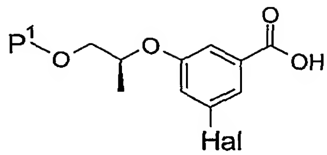
a) hydrolysis of an ester of formula (II) (wherein R is (1-4C)alkyl);



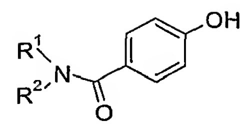
(II)

or

b) reaction of a halo derivative of formula (III) (wherein Hal represents a halogen) with a compound of formula (IV);



(III)



(IV)

wherein in compounds of formula (I) to (IV), R^1 and R^2 are independently selected from hydrogen and (1-6C)alkyl, or R^1 and R^2 together with the nitrogen to which they are attached form a 4- to 7-membered heterocyclic ring, said ring optionally containing 1 further heteroatom selected from O, N and S; and

P^1 is hydrogen or a hydroxy protecting group.

In one aspect of the invention, the compound of formula (I) is made by process a).

In another aspect of the invention, the compound of formula (I) is made by process b).

Suitable conditions for process a) are hydrolysis under mild basic conditions such as the use of sodium hydroxide in tetrahydrofuran. Further suitable conditions include sodium hydroxide in water/methanol at room temperature (Tetrahedron Letters, 46(25), 4311-4313; 2005, and Angewandte Chemie, International Edition, 44(1), 72-75; 2004); and lithium hydroxide in THF/water/methanol at room temperature (Journal of the American Chemical Society, 127(15), 5540-5551; 2005).

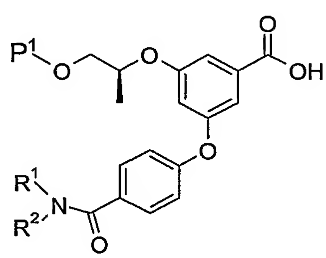
Suitable conditions for process b) are those known to be suitable for Ullman reactions. For example see K Kunz, U Scholz, D Ganzer, *Synlett*, **2003**, 2428-2439, G Mann, C Incarvito, A L Rheingold & J Hartwig, *J. Am. Chem. Soc.*, **1999**, *121*, 3224-3225 and A Aranyos, D W Old, A Kiyomori, J P Wolfe, J P Sadighi & S L Buckwald, *J. Am. Chem. Soc.*, **1999**, *121*, 4369-4378.

Generally, suitable conditions for process b) are use of a high boiling solvent (for example toluene, 1,4-dioxane or DMSO or, for example benzonitrile, dimethylformamide, N-methylpyrrolidone (NMP) or N,N-dimethylpropyleneurea (DMPU)); using a copper or palladium catalyst (for example copper, copper (I) chloride, copper (I) bromide, copper (I) iodide, copper (II) chloride, copper (II) bromide, copper (II) iodide, copper (II) oxide, palladium (II) acetate or bisdibenzylideneacetone palladium (0), or for example copper (I) oxide); a ligand for the catalyst (for example 1,10-phenanthronine, neocuprine, a 1,3-diketone (such as 2,2,6,6-tetramethylheptane-3,5-dione), racemic-2-(di-*t*-butylphsophino)-

1,1'-binaphthyl, 2-(di-t-butylphosphino)biphenyl or 1,1'-bis(di-*t*-butylphosphino)ferrocene; or for example a ligand selected from 8-quinolinol, 1,10-phenanthraline, salicaldioxime, 2,2,6,6-tetramethylheptane-3,5-dione and N,N-dimethylglycine, in particular selected from 2,2,6,6-tetramethylheptane-3,5-dione and N,N-dimethylglycine); and a base (for example inorganic bases such as potassium carbonate, cesium carbonate and organic bases such as sodium *tert*-butoxide) to deprotonate the phenol.

For example process b) may be conducted in NMP or benzonitrile, using copper (I) iodide or copper (I) oxide as catalyst, 2,2,6,6-tetramethylheptane-3,5-dione (or N,N-dimethylglycine, but particularly 2,2,6,6-tetramethylheptane-3,5-dione (TMHD)) as ligand and cesium carbonate as base. It is advantageous to use cesium carbonate with a high surface area and carry out the reaction with vigorous stirring. In another aspect, process b) is carried out in NMP, with copper (I) iodide, TMHD and cesium carbonate.

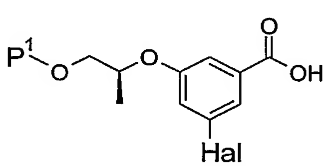
Therefore in another aspect of the invention there is provided a process for making a compound of formula (I),



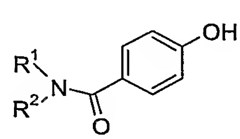
(I)

said process comprising

reaction of a halo derivative of formula (III) (wherein Hal represents a halogen) with a compound of formula (IV);



(III)



(IV)

in the presence of a catalyst, a ligand for said catalyst and a base,

wherein in compounds of formula (I) to (IV), R^1 and R^2 are independently selected from hydrogen and (1-6C)alkyl, or R^1 and R^2 together with the nitrogen to which they are

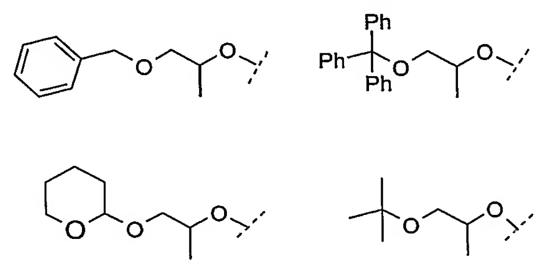
attached form a 4- to 7-membered heterocyclic ring, said ring optionally containing 1 further heteroatom selected from O, N and S; and

P^1 is hydrogen or a hydroxy protecting group.

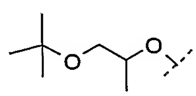
In one aspect, P^1 is a hydroxy protecting group.

Suitable values for hydroxy protecting groups P^1 are any of those known in the art for protecting primary alcohols (see for example "Protective groups in Organic Chemistry" 3rd Edition, TW Greene and PGM Wuts, 1999).

Further suitable values for hydroxy protecting groups P^1 are t-butyl, benzyl, trityl (triphenylmethyl) and tetrahydropyran-2-yl; such that the preferred side chains on compounds of formula (I)-(III) are:



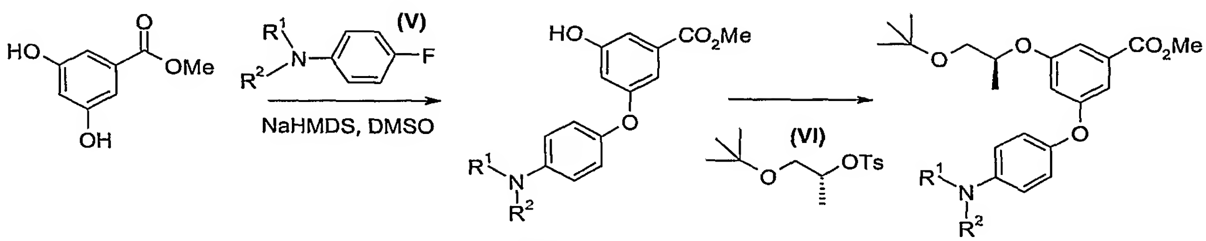
A further suitable protecting group is an allyl ether.

In one aspect, tert-butyl ether:  is a preferred protecting group.

In another aspect, P^1 is hydrogen.

These protecting groups may be removed at a convenient moment in the subsequent synthetic sequence by methods known in the art. For example, a benzyl group may be removed by hydrogenation. A trityl group or a tert-butyl group may be removed by treatment with acid. Suitable acids or acidic conditions for removal of a tert-butyl group are, for example, treatment with hydrochloric acid in methanol, or treatment with amberlyst resin, or treatment with formic acid.

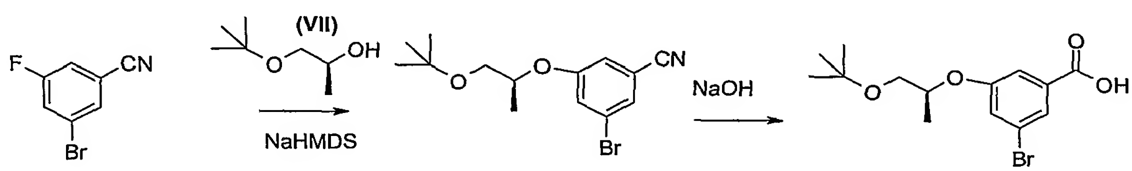
Compounds of formula (II) may be made as illustrated in Scheme 5 (wherein P^1 is tert-butyl).



Scheme 5

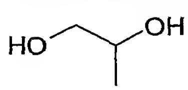
It should be noted that the route illustrated in Scheme 5, although using the same dihydroxymethylbenzoate starting material as the route shown in Scheme 2, advantageously requires fewer steps and fewer protecting groups.

Compounds of formula (III) may be made as illustrated in Scheme 6 (wherein P^1 is tert-butyl).



Scheme 6

Compounds of formula (VI) and (VII) or analogous compounds with other protecting groups can be made by methods known in the art from the commercially available propanediol starting materials, such as:



Compounds of formula (IV) and (V) are either commercially available or can be made from commercially available material by processes known in the art. See also for example our patent applications WO2005/080359 and WO2005/080360.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups. However references to individual alkyl groups such as "propyl" are specific for the straight chain version only and references to individual branched-chain alkyl groups such as *t*-butyl are specific for the branched chain version only. For example, "(1-4C)alkyl" includes methyl, ethyl, propyl, isopropyl and *t*-butyl. An analogous convention applies to other generic terms.

Suitable examples of rings formed by $-NR^1R^2$ include morpholino, piperidinyl, piperazinyl, pyrrolidinyl and azetidinyl. A particular ring formed by $-NR^1R^2$ is azetidinyl.

Further suitable examples of rings formed by $-NR^1R^2$ include homopiperazinyl, homo-morpholino, homo-thiomorpholino (and versions thereof wherein the sulfur is oxidised to an SO or $S(O)_2$ group) and homo-piperidinyl.

Examples of **(1-4C)alkyl** include methyl, ethyl, propyl, isopropyl, butyl and tert-butyl.

In a further aspect of the invention, there is provided a compound of formula (I) as hereinbefore defined .

In a further aspect of the invention, there is provided a compound of formula (II) as hereinbefore defined.

Suitable and particular values for R^1, R^2 and P^1 in compounds of formula (I) and (II) have been given hereinbefore.

Particular compounds of formula (I) include:
3-[4-(azetidin-1-ylcarbonyl)phenoxy]-5-[(1*S*)-2-hydroxy-1-methylethoxy]benzoic acid;
3-[4-(azetidin-1-ylcarbonyl)phenoxy]-5-[(1*S*)-2-*tert*-butoxy-1-methylethoxy]benzoic acid;
3-[4-(azetidin-1-ylcarbonyl)phenoxy]-5-[(1*S*)-2- benzyloxy-1-methylethoxy]benzoic acid;
3-[4-(azetidin-1-ylcarbonyl)phenoxy]-5-[(1*S*)-2-triphenylmethoxy-1-methylethoxy]benzoic acid;
3-[4-(azetidin-1-ylcarbonyl)phenoxy]-5-[(1*S*)-2- tetrahydropyran-2yloxy-1-methylethoxy]benzoic acid.

Particular compounds of formula (II) include
3-[4-(azetidin-1-ylcarbonyl)phenoxy]-5-[(1*S*)-2-hydroxy-1-methylethoxy]benzoic acid methyl ester;
3-[4-(azetidin-1-ylcarbonyl)phenoxy]-5-[(1*S*)-2-*tert*-butoxy-1-methylethoxy]benzoic acid methyl ester;
3-[4-(azetidin-1-ylcarbonyl)phenoxy]-5-[(1*S*)-2- benzyloxy-1-methylethoxy]benzoic acid methyl ester;
3-[4-(azetidin-1-ylcarbonyl)phenoxy]-5-[(1*S*)-2-triphenylmethoxy-1-methylethoxy]benzoic acid methyl ester;
3-[4-(azetidin-1-ylcarbonyl)phenoxy]-5-[(1*S*)-2- tetrahydropyran-2yloxy-1-methylethoxy]benzoic acid methyl ester.

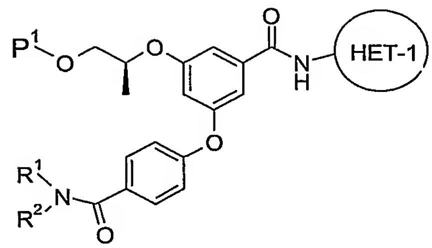
A particular compound of formula (III) is 3-bromo-5-[(1*S*)-2-*tert*-butoxy-1-methylethoxy]benzoic acid.

A particular compound of formula (IV) is 4-(azetidin-1-ylcarbonyl)phenol.

The compounds of formula (I) made by the process of the invention may be reacted to form compounds which are useful as activators of glucokinase (GLK). This activity may be demonstrated by test methods known in the art, for example those given in our patent applications WO 03/015774, WO2005/080359 and WO2005/080360. See also Brocklehurst et al, Diabetes 2004, **53**, 535-541.

Compounds of formula (I) may be further elaborated to make compounds of formula (D) as defined hereinbefore. Processes to carry out this conversion are illustrated in Scheme 4 and in the accompanying examples. Suitably, the carboxylic acid of formula (I) may be coupled with a heterocylic amine derivative by using an appropriate coupling reaction, such as a carbodiimide coupling reaction performed with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDAC) in the presence of dimethylaminopyridine (4-DMAP) in a suitable solvent such as DCM, chloroform or DMF at room temperature; or alternatively with carbonyldiimidazole (CDI) in a suitable solvent such as THF at room temperature; or alternatively using 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) in a suitable solvent such as acetonitrile, for example at 0°C to room temperature; or by a reaction in which the carboxylic group is activated to an acid chloride by reaction with a suitable reagent, such as oxalyl chloride or 1-chloro-N,N,2-trimethyl-prop-1-en-1-amine in the presence of a suitable solvent such as DCM, and where necessary catalytic amount of DMF. The acid chloride can then be reacted with a compound of formula (VIII) (as defined hereinafter) in the presence of a base, such as triethylamine or pyridine, in a suitable solvent such as DCM or pyridine at a temperature between 0°C and 80°C.

In a further feature of the invention, there is provided a process for forming a compound of formula (D)



(D)

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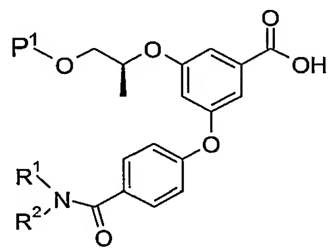
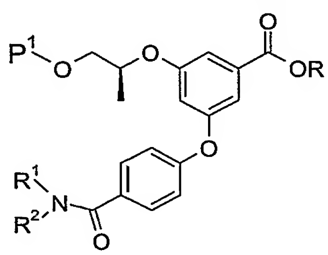
comprising making a compound of formula (I),



(I)

by either step a):

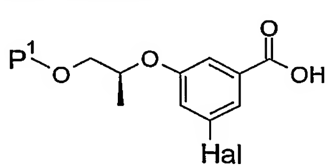
a) hydrolysis of an ester of formula (II) (wherein R is (1-4C)alkyl);



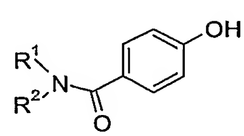
(II)

or step b):

b) reaction of a halo derivative of formula (III) (wherein Hal represents a halogen) with a compound of formula (IV);



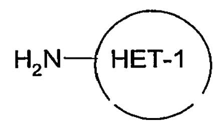
(III)



(IV)

and then

c) reacting the compound of formula (I) with a compound of formula (VIII) to give the compound of formula (D):



(VIII)

wherein R^1 and R^2 are independently selected from hydrogen and (1-6C)alkyl, or R^1 and R^2 together with the nitrogen to which they are attached form a 4- to 7-membered heterocyclic ring, said ring optionally containing 1 further heteroatom selected from O, N and S;

P^1 is hydroxy or a hydroxy protecting group;

HET-1 is an optionally substituted 5- or 6-membered, C-linked heteroaryl ring containing a nitrogen atom in the 2-position.

Suitable conditions for steps a) and b) are as hereinbefore described. Suitably step c) is carried out using coupling conditions as hereinbefore described, such as CDI or CDMT. Optionally, when P^1 is a hydroxy protecting group, the compound of formula (D) may be deprotected to give the corresponding compound wherein P^1 is hydrogen.

For the avoidance of doubt, reference to the group HET-1 containing a nitrogen in the 2-position, is intended to refer to the 2-position relative to the amide nitrogen atom to which the group is attached.

Suitable examples of HET-1 as a 5- or 6-membered, C-linked heteroaryl ring as hereinbefore defined, include thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl and triazolyl.

HET-1 may optionally be substituted with 1 or 2 substituents independently selected from (1-4C)alkyl, halo, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl and di(1-4C)alkylamino(1-4C)alkyl. Preferably HET-1 is optionally substituted by 1 or 2 halo or (1-4C)alkyl substituents, particularly (1-4C)alkyl.

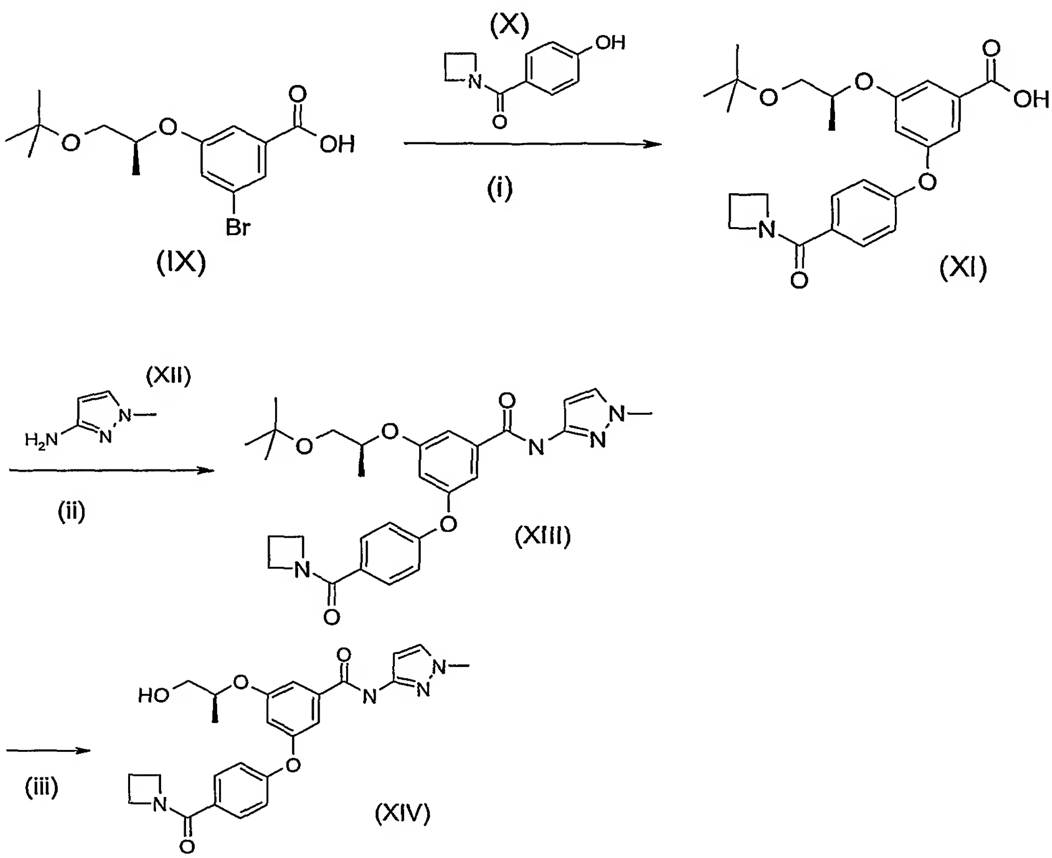
A preferred value for HET-1 is N-methylpyrazolyl.

In another aspect of the invention, there is provided

i) reaction of a compound of formula (IX) with a compound of formula (X) to give a compound of formula (XI);

ii) reaction of the compound of formula (XI) with a compound of formula (XII) to give a compound of formula (XIII); and optionally

iii) reaction of the compound of formula (XIII) to give a compound of formula (XIV).



Suitable conditions for step i) are those given for step b) hereinbefore. Suitable conditions for step ii) are those given for step c) hereinbefore. Suitable conditions for step iii) are those described previously for deprotecting P^1 as a hydroxy protecting group to give a compound wherein P^1 is hydrogen. Further suitable conditions for the each step of the above aspect may be found in the accompanying examples.

In a further aspect of the invention there is provided a compound of formula (I) obtained by the process of the invention. In another aspect of the invention there is provided a compound of formula (I) obtainable by the process of the invention.

It will be appreciated that methods for, for example purification, of the compounds in the Examples below are illustrative and alternatives may be used where the skilled person would deem them appropriate.

The invention will now be illustrated by the following Examples, in which, unless otherwise stated:

(i) evaporations were carried out by rotary evaporation in *vacuo* and work-up procedures were carried out after removal of residual solids such as drying agents by filtration;

(ii) operations were carried out at room temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon or nitrogen;

(iii) yields are given for illustration only and are not necessarily the maximum attainable;

(iv) the structures of the end-products were confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; proton magnetic resonance chemical shift values were measured on the delta scale and peak multiplicities are shown as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; q, quartet, quin, quintet;

(v) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), high-performance liquid chromatography (HPLC), infra-red (IR) or NMR analysis.

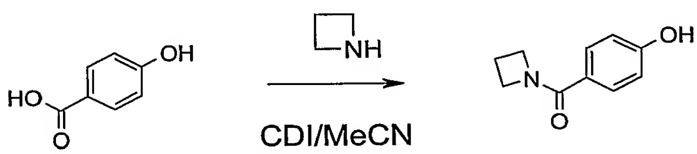
Abbreviations

DCM	dichloromethane
DMSO	dimethyl sulphoxide
DMF	dimethylformamide
HPLC	high pressure liquid chromatography
LCMS	liquid chromatography / mass spectroscopy
NMR	nuclear magnetic resonance spectroscopy
$CDCl_3$	deuterochloroform
MTBE	methyltert-butyl ether
THF	tetrahydrofuran
NMP	N-methylpyrrolidone

TFA	trifluoroacetic acid
EtOAc	ethyl acetate
CD_3OD	perdeuteromethanol
MeOH	methanol
RT	room temperature

Example 1

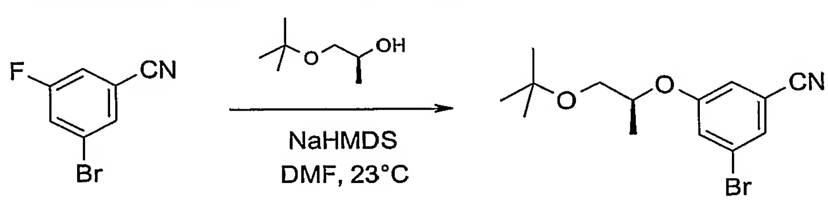
4-(Azetidin-1-ylcarbonyl)phenol



1,1-Carbonyldiimidazole (95.57mmol; 16.57g) was charged to a 250 mL round bottomed flask purged with nitrogen, acetonitrile (72 mL) was added, to form a mobile white slurry. 4-Hydroxybenzoic acid (86.88mol; 12.00g) was added in portions over 30 minutes to give clear yellow solution, which then became a slurry after approximately 15 minutes. The slurry was heated to 50°C and azetidine (104.25mmo; 5.95g) in acetonitrile (10 mL) was added drop wise over 10 minutes. Further azetidine (17.38mmol; 992.08mg) was added in acetonitrile (12 mL) and the reaction mixture was heated to 50°C for a further hour. The precipitated product (10g, 65% yield) was isolated by filtration and washed with acetonitrile (15 mL) and then dried in a vacuum oven at 40°C.

^{1}H NMR (400 MHz, d^6-DMSO) 9.96 (s, 1H), 7.48 (d, 2H), 6.78 (d, 2H), 4.28 (s, 2H), 4.0 (s, 2H), 2.23 (quintet, 2H)

3-Bromo-5-[(1*S*)-2-*tert*-butoxy-1-methylethoxy]benzonitrile

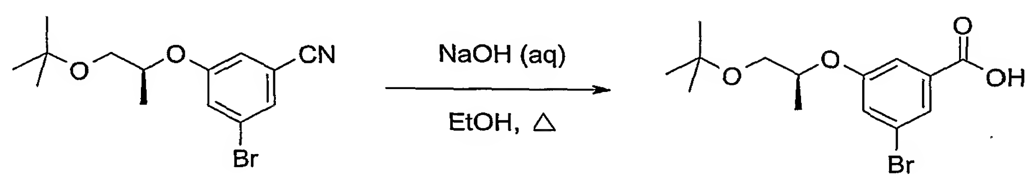


All glassware was oven dried and cooled under nitrogen - inertion was maintained throughout experiment.

To a stirred suspension of sodium bis(trimethylsilyl)amide (74.25 mmol; 14.33 g) in DMF (150 mL) at 23°C was added (S)-*tert*-butoxy-2-propanol (74.25 mmoles, 9.82 g) over 15 minutes. A slight exotherm was observed (cold water cooling bath applied). A solution of 3-bromo-5-fluorobenzonitrile (49.50 mmol, 10.0 g) in DMF (40 mL) was added over 15 minutes with cold water bath still present. An exotherm (3°C) was observed and the mixture turned from yellow to brown. DMF (10 mL) was added and the mixture stirred at ambient temperature for 1 hour. The reaction was quenched by addition of aqueous HCl (2M, 100 mL), maintaining temperature below 25°C . The mixture was diluted with water (200 mL) and extracted with 2:1 EtOAc / MTBE (3 x 200 mL). The organic layers were combined, washed with water (3 x 200 mL) and dried over $MgSO_4$, and the solvent removed *in vacuo* affording the title compound as an orange oil (17.4 g). Further drying *in vacuo* at 23°C gave the title product (15.5 g, ~100%).

^1H NMR: (400 MHz, $CDCl_3$) δ 7.38 - 7.35 (m, 1H), 7.34 - 7.31 (m, 1H), 7.18 - 7.14 (m, 1H), 4.51 - 4.41 (m, 1H), 3.53 (dd, 1H), 3.42 (dd, 1H), 1.31 (d, 3H), 1.17 (s, 9H).

<u>3-Bromo-5-[(1*S*)-2-*tert*-butoxy-1-methylethoxy]benzoic acid</u>



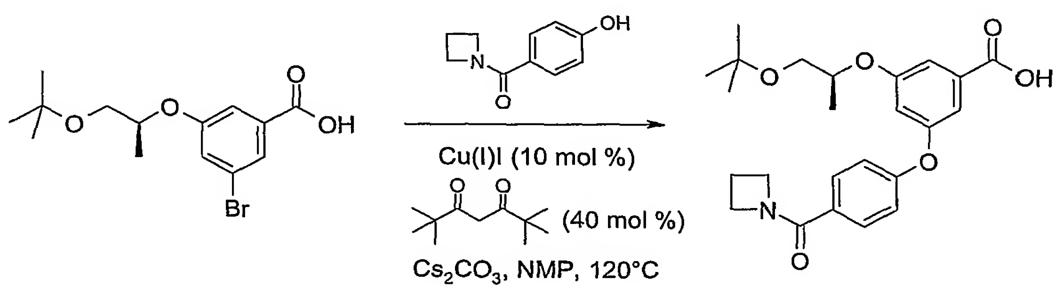
To a stirred solution of 3-bromo-5-[(1*S*)-2-*tert*-butoxy-1-methylethoxy]benzonitrile (1.00 equiv, 42.60 mmoles, 13.30 g) in ethanol (135 mL) and water (13.30 mL) was added sodium hydroxide liquor (46/48 % w/w, 5213.0 mmol, 12.10 mL, 18.27 g). The resultant yellow solution was heated to reflux for 1 hour and the solvent removed *in vacuo* to give a wet orange solid. The mixture was partitioned between water (150 mL) and MTBE (100 mL). The coloured upper organic phase contained two layers and was separated from the lower aqueous phase. **Note:** high solubility of the product sodium salt in the organic phase; only minor loss to the aqueous layer. The organic layers were concentrated to give a gummy orange solid (approx 18 g). The residue was partitioned between aqueous HCl (1M, 200 mL) and MTBE (150 mL). The Layers were separated and the aqueous phase

further extracted with MTBE (100 mL). The organic phases were combined, washed with saturated brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give an orange gum (12.85 g), which solidified on standing.

The recovered solid (11.7 g) was stirred in *iso*-hexane (60 mL) at 23°C for 35 minutes, isolated by buchner filtration, displacement washed with *iso*-hexane (2 x 10 mL) and dried at ambient temperature under nitrogen to give a pale yellow, free flowing solid (8.60 g, 61 % yield). The mother liquors were concentrated *in vacuo* and stirred with *iso*-hexane (5 mL) for 2 hours. The product was collected by filtration, displacement washed with *iso*-hexane (2 x 5 mL) and dried at ambient temperature under nitrogen to give a pale yellow, free flowing solid (1.60 g, 11 % yield).

^{1}H NMR: (400 MHz, CD_3OD) δ_H 7.68 (s, 1H), 7.55 (s, 1H), 7.35 (s, 1H), 4.58 - 4.48 (m, 1H), 3.55 (dd, 1H), 3.47 (dd, 1H), 1.30 (d, 3H), 1.18 (s, 9H).

3-[4-(Azetidin-1-ylcarbonyl)phenoxy]-5-[(1*S*)-2-*tert*-butoxy-1-methylethoxy]benzoic acid

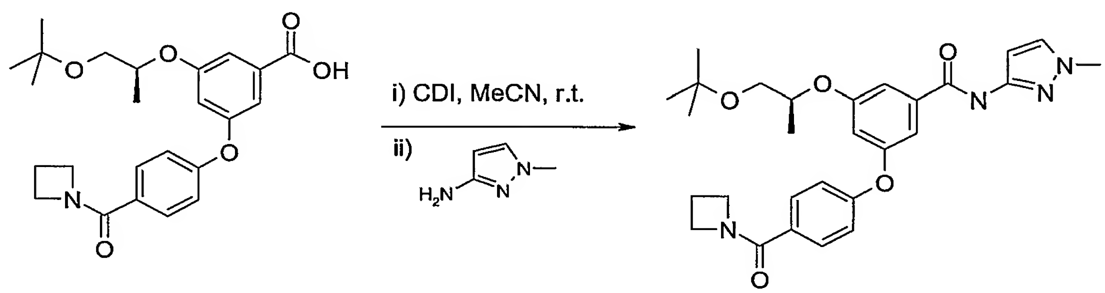


An oven dried, screw capped reaction tube, cooled and purged under nitrogen, containing 3-bromo-5-[(1*S*)-2-*tert*-butoxy-1-methylethoxy]benzoic acid (1.8 mmol, 581.3 mg), 4-(azetidin-1-ylcarbonyl)phenol (2.6 mmol, 471.9 mg), cesium carbonate (2.6 mmol, 856.3 mg), copper(I) iodide (163.3 µmol; 31.1 mg), 2,2,6,6-tetramethyl- 3,5-heptanedione (702.0 µmol, 146.7 µL) and NMP (5.8 mL) was flushed with nitrogen and sealed. The resultant brown suspension was stirred and heated at 112°C for 16 hours. The reaction mixture was further heated at 120°C for 6.5 hours and cooled to ambient temperature. Water was added (10 mL) to dissolve inorganic species and the reaction mixture stirred with MTBE / EtOAc (1:1, 10 mL) for 5 minutes and separated. The aqueous layer was acidified with HCl (2M, 8.8 mmol, 4.4 mL), stirred with MTBE / EtOAc (1:1, 20 mL) for 5 minutes and the layers separated. The organic layer was further washed with aqueous HCl (2M, 8.8 mmol, 4.4

mL) and the layers separated. The organic phase was washed with saturated brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a red gum (767 mg). The residue was purified by column chromatography using EtOAc / DCM / MeOH (10:10:1) to give the title compound as a pale pink solid (493 mg, 66% yield).

^{1}H NMR: (400 MHz, CD_3OD) δ_H 7.67 (d, 2H), 7.41 (m, 1H), 7.19 (m, 1H), 7.06 (d, 2H), 6.87 (t, 1H), 4.56 – 4.45 (m, 1H), 4.41 (t, 2H), 4.19 (t, 2H), 3.55 (dd, 1H), 3.47 (dd, 1H), 2.37 (quintet, 2H), 1.29 (d, 3H), 1.17 (s, 9H).

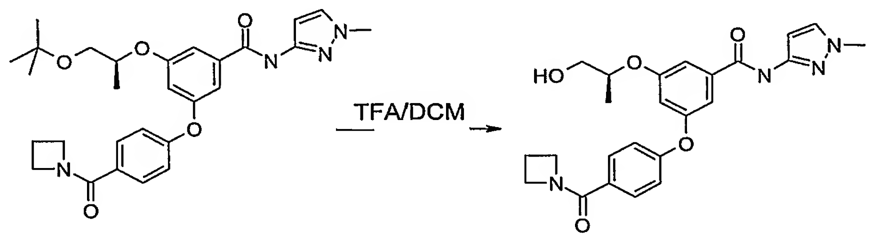
Example 2: 3-[4-(Azetidin-1-ylcarbonyl)phenoxy]-5-[(1*S*)-2-*tert*-butoxy-1-methylethoxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



3-[4-(Azetidin-1-ylcarbonyl)phenoxy]-5-[(1*S*)-2-*tert*-butoxy-1-methylethoxy]benzoic acid (853.8 µmol, 365.0 mg) was added portionwise over 30 minutes to a colourless, stirred solution of 1,1'-carbonyldiimidazole (11.1 mmol, 180.3 mg) in acetonitrile (3.5 mL) in an oven dried tube under a nitrogen atmosphere at 25°C. The resultant pink solution was stirred at 25°C for 35 minutes. The reaction solution was then heated to 50°C, 1-methyl-3-aminopyrazole (1.3 mmol, 130µL) was added in a single portion and the mixture stirred overnight at temperature. The solvent was removed *in vacuo* to give a red oil (700 mg). The residue was partioned between MTBE (10 mL) and saturated sodium hydrogen carbonate solution (6 mL). A red oily interface was present. EtOAc (5 mL) was added and the two phase mixture was stirred for 5 minutes and the interface disappeared. The organic phase was further washed with saturated sodium hydrogen carbonate solution (5 mL), water (5 mL), saturated brine (10 mL), and was then dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a pale yellow / brown foam (385 mg, 89 % yield).

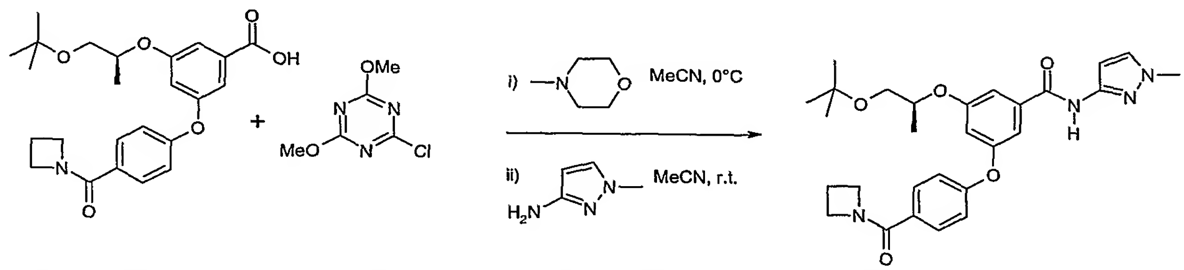
^{1}H NMR: (400 MHz, CD_3OD) δ_H 7.68 (d, 2H), 7.48 (d, 1H), 7.34 (s, 1H), 7.17 (s, 1H), 7.08 (d, 2H), 6.84 (t, 1H), 6.57 (d, 1H), 4.63 - 4.49 (m, 1H), 4.41 (t, 2H), 4.19 (t, 2H), 3.81 (s, 3H), 3.56 (dd, 1H), 3.48 (dd, 1H), 2.36 (quintet, 2H), 1.30 (d, 3H), 1.17 (s, 9H).

3-[4-(Azetidin-1-ylcarbonyl)phenoxy]-5-[(1*S*)-2-hydroxy-1-methylethoxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



3-[4-(Azetidine-1-carbonyl)-phenoxy]-5-((S)-2-tert-butoxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl)-benzamide (101.3 µmol; 51.3 mg) was charged to a small screw capped reaction tube. DCM (500.0 µL) was added the reaction mixture followed by TFA (506.3 µmol; 38.3 µL; 57.7 mg), the reaction mixture was stirred at ambient temperature for 18 hours. HPLC analysis showed no reaction after this time. The reaction mixture was heated to 40°C, extra TFA (506.3 µmol; 38.3 µL; 57.7 mg) was added to the reaction tube and the mixture was held at 40°C for 18 hours. Water (1 mL) was added to the reaction tube followed by sodium hydroxide (2M) (1.0 mmol; 506.3 µL; 526.6 mg). MTBE (4 mL) was added and the mixture was stirred for 5 minutes. An oily gum had formed which was dissolved by addition of EtOAc (2 mL). The two layers were separated and the upper organic layer was retained, the aqueous was extracted again with EtOAc (2 x 5 mL). The combined organic layers were washed with saturated brine (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a colourless oil (35 mg, 75.7% yield).
^{1}H NMR: (400 MHz, CD_3OD) δ_H 7.64 (d, 2H), 7.45 (d, 1H), 7.32 (s, 1H), 7.15 (s, 1H), 7.04 (d, 2H), 6.83 (s, 1H), 6.56 (d, 1H), 4.53 (sextet, 1H), 4.37 (t, 2H), 4.15 (t, 2H), 3.77 (s, 3H), 3.64 (d, 2H), 2.32 (quintet, 2H), 1.26 (d, 3H).

Example 3: 3-[4-(Azetidin-1-ylcarbonyl)phenoxy]-5-[(1*S*)-2-*tert*-butoxy-1-methylethoxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



3-[4-(Azetidin-1-ylcarbonyl)phenoxy]-5-[(1*S*)-2-*tert*-butoxy-1-methylethoxy]benzoic acid (6.18 mmol, 2.64 g) and acetonitrile (18.5 mL) were charged to a vessel. The contents were stirred and cooled to 0°C. 2-Chloro-4,6-dimethoxy-1,3,5-triazine (6.78 mmol, 1.19 g) was added to the slurry followed by an addition of N-methylmorpholine (8.11 mmol, 0.82 g), added over 20 minutes. The reaction was held for approximately 1 hour at 0°C and allowed to warm up to ambient. N-methylaminopyrazole (6.79 mmol, 0.66 g) was added over 20 minutes and the reaction held at ambient temperature until the reaction was complete. Water (7 mL) was added to the reaction mixture and the acetonitrile removed by distillation at reduced pressure. Ethyl acetate (32 mL), water (7 mL) and sodium bicarbonate solution (10% by weight, 26 mL) were added to the resultant slurry. The bi-phasic liquor was separated and the ethyl acetate phase sequentially washed with further sodium bicarbonate (10% by weight, 13 mL), water (13 mL), 2M hydrochloric acid (2 x 13 mL), and then with water (2 x 13mL). The washed organic phase was azeodistilled at reduced pressure, removing water and solvent, to give a light brown foam (2.9g, 90% yield).

^{1}H NMR: (400 MHz, d_6-DMSO) δ_H 10.85 (1H, s), 7.65 (2H, d), 7.58 (1H, d), 7.45 (1H, s), 7.21 (1H, s), 7.05 (2H, d), 6.81 (1H, t), 6.54 (1H, d), 4.61 (1H, sextet), 4.30 (2H, br t), 4.02 (2H, m), 3.75 (3H, s), 3.47 (1H, dd), 3.39 (1H, dd), 2.23 (2H, quintet), 1.23 (3H, d), 1.10 (s, 9H).

Example 4: 3-[4-(Azetidin-1-ylcarbonyl)phenoxy]-5-[(1*S*)-2-*tert*-butoxy-1-methylethoxy]benzoic acid

3-Bromo-5-[(1S)-2-tert-butoxy-1-methylethoxy]benzoic acid (9.78 g, 29.51 mmol), 4-(azetidin-1-ylcarbonyl)phenol (7.84 g, 44.70 mmol), cesium carbonate (19.23 g, 59.03

mmol) and NMP (78 mL) were mixed together in a dry reaction flask and agitated overnight under a nitrogen atmosphere. Copper (I) iodide (0.56 g, 2.95 mmol), 2,2,6,6-tetramethylheptane-3,5-dione (2.18 g, 11.81 mmol) and an NMP line wash (20 mL) were added under a nitrogen atmosphere. The reaction mixture was heated to 125°C for approximately 20 hours.

The reaction mixture was then cooled to 22°C, and diluted with MTBE (59 mL) and water (59 mL). Further 2,2,6,6,-tetramethylheptane-3,5-dione (5.55g, 29.5mmol) was added and the upper layer separated off from the reaction mixture. The lower aqueous layer was extracted with MTBE (59 mL) and 2,2,6,6,-tetramethylheptane-3,5-dione (5.55 g, 29.5 mmol) twice more.

The aqueous layer was then acidified using 2M hydrochloric acid (59 mL), and the majority of the mixture extracted into ethyl acetate (98 mL). The aqueous layer was re-extracted with a second smaller portion of ethyl acetate (19.6 mL). The ethyl acetate layers were combined and the residual NMP removed by three water washes (98 mL).

Water (98 mL) was then added to the ethyl acetate solution of the product, and potassium carbonate (4.89g, 35.42 mmol) was added. The lower aqueous phase containing the product was separated off, and the organic layer discarded. Ethyl acetate (98 mL) was added to the aqueous phase followed by 2M hydrochloric acid (37 mL). The layers were separated and the lower aqueous phase was discarded.

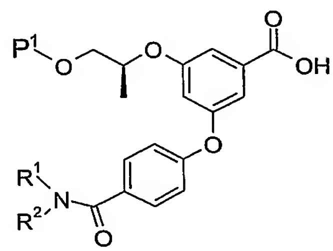
Water (98 mL) was added to the ethyl acetate layer, and potassium carbonate (4.89 g, 35.42 mmol) was added. The lower aqueous phase containing the product was separated off, and the organic layer discarded. Ethyl acetate (98 mL) was added to the aqueous phase followed by 2M hydrochloric acid (37 ml). The layers were separated and the lower aqueous phase was discarded.

Water (98 mL) was added to the ethyl acetate layer, and potassium carbonate (4.89g, 35.42 mmol) was added. The lower aqueous phase containing the product was separated off, and the organic layer discarded. MTBE (98 mL) was added to the aqueous layer. The mixture was warmed to 50°C and 2M hydrochloric acid (37 mL) was added. The layers were separated and the lower aqueous phase was discarded. The MTBE layer was washed with a small amount of water (20 mL) at 50°C, then was distilled to remove water, passed through a fine filter, cooled to 22°C and seeded. Isohexane (147 mL) was added to the crystalline slurry. The mixture was cooled to -10°C, filtered, and washed with 1:2 MTBE:

isohexane (29 mL). The isolated product was dried in the vacuum oven at 50°C (yield at 100% strength = 58.4%).

Claims

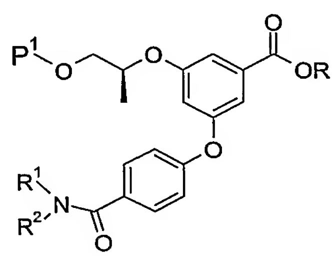
1. A process for making a compound of formula (I),



(I)

said process comprising either:

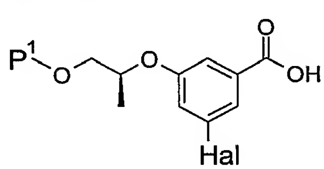
a) hydrolysis of an ester of formula (II) (wherein R is (1-4C)alkyl);



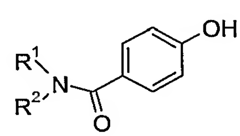
(II)

or

b) reaction of a halo derivative of formula (III) (wherein Hal represents a halogen) with a compound of formula (IV);



(III)



(IV)

wherein in compounds of formula (I) to (IV), R^1 and R^2 are independently selected from hydrogen and (1-6C)alkyl, or R^1 and R^2 together with the nitrogen to which they are attached form a 4- to 7-membered heterocyclic ring, said ring optionally containing 1 further heteroatom selected from O, N and S; and

P^1 is hydrogen or a hydroxy protecting group.

2. A process as claimed in Claim 1, wherein the compound of formula (I) is made by process b).

3. A process as claimed in Claim 1 or Claim 2, wherein P^1 is t-butyl.

4. A process as claimed in any one of the preceding claims wherein R^1 and R^2 together with the nitrogen to which they are attached form a 4- to 7-membered heterocyclic ring.

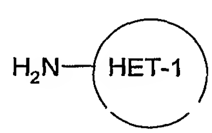
5. A process as claimed in Claim 4 wherein R^1 and R^2 together with the nitrogen to which they are attached form an azetidinyl ring.

6. A process as claimed in any one of claims 1 to 5 wherein process b) is carried out in the presence of copper(I) iodide or copper(I) oxide as catalyst.

7. A process as claimed in any one of claims 1 to 6 wherein process b) is carried out in the presence of 2,2,6,6-tetramethylheptane-3,5-dione.

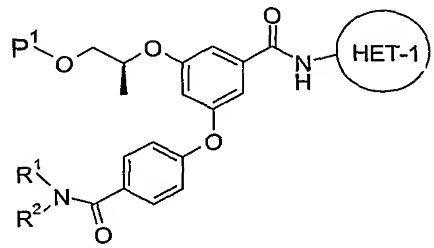
8. A process as claimed in any one of claims 1 to 7 wherein process b) is carried out in NMP or benzonitrile.

9. A process as claimed in Claim 1, wherein the compound of formula (I) is then reacted with a compound of formula (VIII)



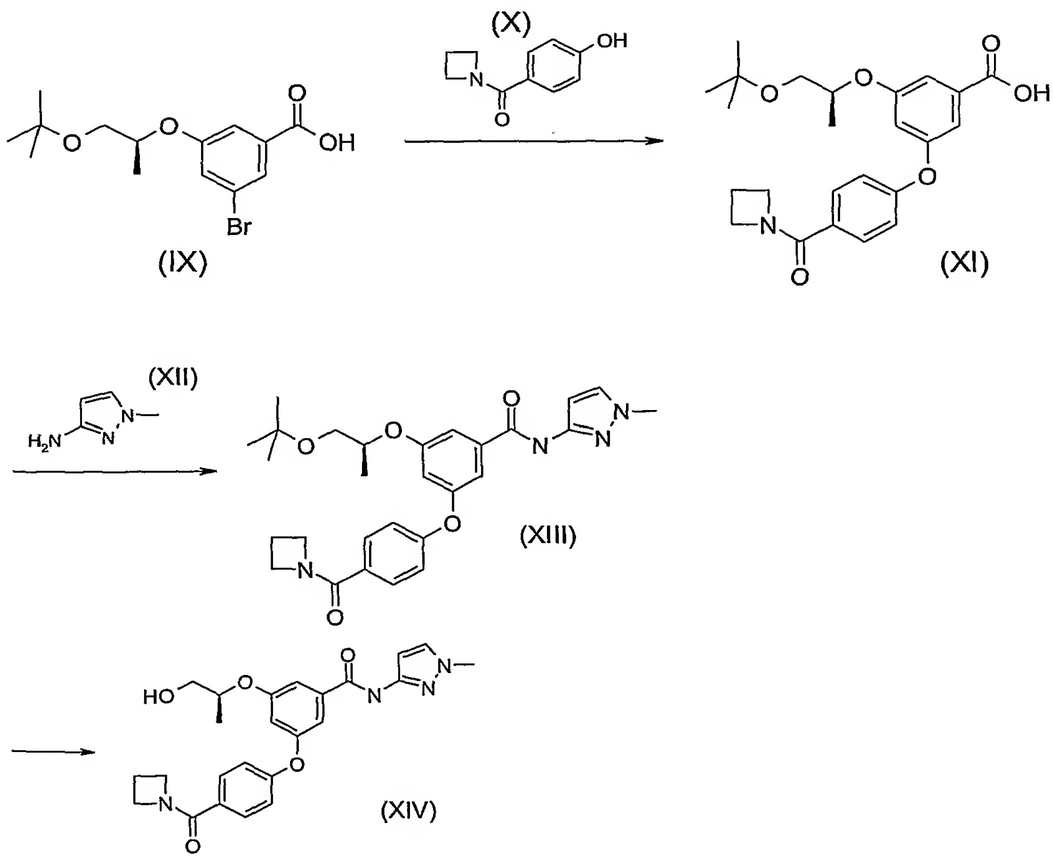
(VIII)

to form a compound of formula (D).



(D)

10. A process as claimed in Claim 9 comprising:
i) reaction of a compound of formula (IX) with a compound of formula (X) to give a compound of formula (XI);
ii) reaction of the compound of formula (XI) with a compound of formula (XII) to give a compound of formula (XIII); and optionally
iii) reaction of the compound of formula (XIII) to give a compound of formula (XIV).



11. A process as claimed in Claim 10 wherein step i) is carried out in the presence of copper(I) iodide or copper(I)oxide as a catalyst.

12. A process as claimed in Claim 11 wherein step i) is carried out in the presence of 2,2,6,6-tetramethylheptane-3,5-dione as a ligand for the catalyst.

13. A compound of formula (II) as defined in Claim 1, selected from:

3-[4-(azetidin-1-ylcarbonyl)phenoxy]-5-[(1*S*)-2-hydroxy-1-methylethoxy]benzoic acid methyl ester;

3-[4-(azetidin-1-ylcarbonyl)phenoxy]-5-[(1*S*)-2-*tert*-butoxy-1-methylethoxy]benzoic acid methyl ester;

3-[4-(azetidin-1-ylcarbonyl)phenoxy]-5-[(1*S*)-2- benzyloxy-1-methylethoxy]benzoic acid methyl ester;

3-[4-(azetidin-1-ylcarbonyl)phenoxy]-5-[(1*S*)-2-triphenylmethoxy-1-methylethoxy]benzoic acid methyl ester; and

3-[4-(azetidin-1-ylcarbonyl)phenoxy]-5-[(1*S*)-2- tetrahydropyran-2yloxy-1-methylethoxy]benzoic acid methyl ester.